Can We Measure, Quantify and Model the Biomechanics of the Cornea?

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Is biomechanics important?

A corneal perspective...

- **Safety and predictability** of corneal surgery depends on surgical variables AND mechanical status of cornea

- Diagnosis of early ectasias and treatment of progression using biomechanical interventions

- Corneal properties affect IOP measurement and may interact with glaucoma risk

- The biomechanical properties of normal cornea are poorly understood
Can we measure corneal biomechanical behavior?
Measuring the elastic modulus

Nonlinear Elastic Behavior

Dupps & Doehring, 2006
Seismic corneal stiffness interrogation

RAYLEIGH WAVE

Direction of Propagation

Particle Motion

Wave animation courtesy of Professor Larry Braile, Purdue U
Surface wave elastometry

- **Sonic Eye**® (PriaVision, Menlo Park CA)
  - Measures time-of-flight of low frequency wave over 4.5 mm distance
  - Elastic modulus related to $\rho V^2$

Dupps et al, JRS 2007
Spatial differences in corneal stiffness

Dupps et al, ARVO 2006
Preferred collagen organization leads to nonuniformity of stiffness

Meek et al, IOVS 2005

Boote et al, J Struct Biol 2005

Dupps & Doehring, 2005
Surface wave elastometry

- **Advantages**
  - Nondestructive test
  - Directional and some spatial resolution
  - Simple method, repeatable perturbation

- **Disadvantages**
  - Contact artifact
  - Surface bias
  - Tear film interference
Viscoelasticity

- Property of all biological tissues
- Viscous domain (fluid property) adds time and rate dependence ("history") to stress response
Ocular Response Analyzer®: a high-speed *history* of the bending response

Image courtesy of Reichert
ORA signal and corneal hysteresis (CH)

Luce, JCRS 2005

CH reflects viscous damping capacity
Does CH tell the whole story?

![Box-and-whisker plots](image)

**Figure 3.** Box-and-whisker plots (median and interquartile range) of hysteresis in normal and keratoconic eyes.

Luce, JCRS 2005
Does CH tell the whole story?
ORA signal and Hysteresis Loop Area

Hallahan et al, ARVO 2008
CH and HLA in keratoconus

- Retrospective analysis of signals on 54 keratoconic and 54 normal eyes from same center/device (R. Ambrosio, Jr.)

Hallahan et al, ARVO 2008
HLA vs. CH and CRF in keratoconus

Hallahan et al, ARVO 2008
Does the ORA measure corneal hysteresis?

- CH differs between whole globes and in mounted corneo-scleral explants from the same eye with unaltered corneal thickness, IOP or intrinsic stiffness ($p<0.001$) (Dupps & Ramos-Esteban, 2007)

- So CH is affected by alterations in the ocular shell
  - Implications in glaucoma where peripapillary scleral thickness & properties are important
  - Correlation between glaucoma progression and low CH (Congdon et al, AJO 2006)
Ocular Response Analyzer

Advantages
- Nondestructive test
- Noncontact
- Simple method
- Commercially available now

Disadvantages
- Variable air pressure
- Diagnostic overlap*
- 1-D displacement resolution*
Stiffness is a dynamic property inferred from spatial response to stress

Courtesy J. Ophir
OCT Elastography

\[ C(x, y) = \frac{\sum_{x,y} [M(x, y) - \bar{M}] [N(x, y) - \bar{N}]}{\left\{ \sum_{x,y} [M(x, y) - \bar{M}] \sum_{x,y} [N(x, y) - \bar{N}] \right\}^{0.5}} \]

2x oversampling, 4 um lateral & 8 um axial sampling densities

2 human globes from the same donor

Ford et al, SPIE 2006 and Dupps et al, ARVO 2007
OCT strain mapping during IOP decrease
OCT elastography

Predominantly radial (axial) displacement in normal cornea

Dupps et al, ARVO 2007
Map of peri-incisional vector displacements in a cornea incised to 300 um depth shows more inhomogeneous strain with directional reversals and significant lateral strain not observed in normal corneas.
OCT elastography in keratoconus

with C. Roberts, G. Grabner
Optical elastography

- Advantages
  - Nondestructive, noncontact
  - Full 3-D spatial resolution
  - High resolution

- Disadvantages
  - Complex method
  - Computationally intensive
  - Large strain decorrelation
FEM: A computational approach to biomechanical problems

- Geometry and spatial relationships
  - Imaging (MRI and topography)
- Meshing
  - Represent substructure
- Material property specification
  - Define viscoelastic behavior
- Model solution and the reality check
  - Simulation and optimization
Finite element method

Dupps & Sinha Roy, ARVO 2008
Modeling the flap and interface

Figure 1B: FEM mesh in the central and paracentral zone of the cornea. The LASIK flap can be seen as a single layer.
Effect of altering corneal hyperelastic properties within reported range

Hyperelastic properties “weak”

Hyperelastic properties “strong”

Dupps & Sinha Roy, ARVO 2008
Scleral and corneal stiffness affect response to LASIK

- In a whole-eye model, biomechanical and optical behaviors depend upon corneal elasticity *relative to extracorneal structures*

- Patient-to-patient variations in the corneoscleral stiffness relationship (disease, surgery, crosslinking) can affect:
  - steady-state corneal shape
  - refractive outcomes after LASIK
Fig 1a: FEM mesh

Vertical meridian
Diagonal meridian
Horizontal meridian

Fig 1b: Displacement contour of the posterior cornea at IOP = 10 mmHg.
All values are in mm.

Sinha Roy & Dupps, ARVO 2008
Conclusions

- As measurement precision of wavefront and corneal geometry approaches the limits of biological variability, patient-specific tissue properties matter.

- Even as surgical precision approaches perfection, tissue responses will vary from person to person.

- Patient-specific biomechanical measurement, modeling and even modification provides tools for better diagnosis, surgical planning, & corneal and ocular disease risk modification.
The goal: closing the loop...

- Macrostructural geometry
- Substructural meshing
- Load
- Simulation
- Stress/strain/geometric solutions
- Refine
- Material properties
- Comparison to empirical data
Thank you
Can we model biomechanical behavior?
Can we model biomechanical behavior?

- VE material testing
How can we model biomechanical behavior?

Sinha Roy et al, 2007

\[
E_\infty \left[ 1 + \sum_m \beta_m \left( \frac{t}{\tau_m} \right) \right]
\]
Corneal stiffness affects IOP measurement

- 2 human globes
- Intra-vitreal IOP maintained at 30 mmHg
- Crosslinking with glutaraldehyde 4%, 45 min.

<table>
<thead>
<tr>
<th></th>
<th>Before CCL</th>
<th>After CCL</th>
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<tbody>
<tr>
<td>Central Wave Velocity (m/s)</td>
<td>80 ± 3</td>
<td>145 ± 5</td>
</tr>
<tr>
<td></td>
<td>79 ± 4</td>
<td>147 ± 5</td>
</tr>
<tr>
<td>Pneumo (mmHg)</td>
<td>33.5</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>31</td>
<td>79.5</td>
</tr>
<tr>
<td>Tonopen (mmHg)</td>
<td>35</td>
<td>87</td>
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<tr>
<td></td>
<td>36</td>
<td>89</td>
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Dupps et al, JRS 2007
Collagen crosslinking and central islands

- Mount
  - Inflate to 15 mmHg
  - Remove epithelium

- 40 min, 15% dextran
  - 20 min, 4% GTA
- Sham PTK
- PTK
- Soak Phase

- 60 min, 15% dextran
- Sham PTK
- PTK
- Soak Phase
Collagen crosslinking, central islands, hydration behavior, and ablation rate

<table>
<thead>
<tr>
<th></th>
<th>Crosslinked Group</th>
<th>Control Group</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td><strong>Preop central thickness (um)</strong></td>
<td>564 ± 41</td>
<td>561 ± 40</td>
<td>.83</td>
</tr>
<tr>
<td><strong>Thickness loss with ablation (um)</strong></td>
<td>86 ± 25</td>
<td>79 ± 15</td>
<td>.41</td>
</tr>
<tr>
<td><strong>Thickening with soak (um)</strong></td>
<td>-2 ± 17</td>
<td>+117 ± 27</td>
<td>&lt;.001</td>
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